The Assessment of Structural and Functional Test Results for Early Detection of Hydroxychloroquine Macular Toxicity

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Abstract

Purpose

To assess structural (optical coherence tomography, fundus autofluorescence) and functional (contrast sensitivity and visual field) test results used for detecting early retinal changes in patients who were using oral hydroxychloroquine.

METHODS

Patients who were taking oral hydroxychloroquine for at least one year were divided into two groups in accordance with the duration of drug use. Group 1 and 2 comprised patients with drug use exceeding 5 years and 1–5 years, respectively. Besides, drug-free control group was composed. Upon full ophthalmic examination, the mean retinal nerve layer thickness (RNFL), central macular thickness (CMT), ganglion cell-inner plexiform layer thickness (GC-IPL), static 10 – 2 visual field, fundus autofluorescence (FAF) imaging, and contrast sensitivity tests were performed and statistically compared between groups.

RESULTS

RNFL thickness was found to be statistically significantly lower in the median and temporal quadrant than in the control group. No significant difference was found between the groups in the other quadrants. The GC-IPL sectoral and mean thickness were found to be statistically lower in all quadrants as compared to the control group in the patient groups. CMT was also found to be similar in all three groups. There was no significant difference between the groups in visual field parameters. While macular FAF images were significantly higher in the drug users than in the control group, no significant difference was found between the three groups in foveal FAF images. Contrast sensitivity measurements were significantly lower in the patient groups than in the control group at all spatial frequencies except 6 and 18 cycles / degree.

CONCLUSIONS

The combined use of structural and functional tests in patients using hydroxychloroquine provides useful information in detecting early retinal changes.

Introduction

Hydroxychloroquine (HCQ) and chloroquine have been used for the treatment of rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and many other autoimmune system diseases because of their relatively fewer toxic side effects (1). These two drugs are known to cause similar types of maculopathy. While the first report on the toxicity of chloroquine was published in 1959, the first such report about hydroxychloroquine toxicity was published 1967 (2, 3). In recent years, hydroxychloroquine has been used widely because of the lesser toxic effects (4).

According to previous studies, HCQ had toxic effects on the ganglion cell layer and impaired perifoveal photoreceptors, possibly due to the disruption of retina pigment epithelium (RPE). Lysosomal functions of RPE were suggested to diminish, thus explaining the accumulation of lipofuscin (5–8).

The patients with HCQ retinal toxicity might either be asymptomatic or exhibit symptoms such as reading difficulties and color vision impairment. Granular pigmentation in the macular region and the loss of foveal reflex are the most common early findings of HCQ toxicity. In later stages, Bull's eye maculopathy is developed. If intake of HCQ is not stopped, peripheral pigmentation occurs and these effects may be irreversible (9).

According to American Academy of Ophthalmology (AAO), the patient should be examined before using medication. In order to exclude the accompanying maculopathy; if the patient does not have any major risk factors and the patient is using recommended doses of HCQ medication, annual imaging is recommended after five-year drug use. Primary screening tests are automated visual field and Enhanced Depth Imaging Optical Coherence Tomography (EDI-OCT). AAO also advised examining beyond the central macula in Asian patients. Multifocal electroretinogram (mfERG) can provide objective verification for visual fields and fundus autofluorescence (FAF) topographically reveals damage (10).

In our study, we aimed to evaluate the effectiveness of structural tests including; retinal nerve layer thickness (RNFL), central macular thickness (CMT), ganglion cell-inner plexiform layer thickness (GC-IPL), FAF, and functional tests including 10 – 2 visual field (VF) test, best corrected visual acuity and contrast sensitivity in patients who have used HCQ at least one year and compare these test results between patients and control subjects.

Material And Method

This study was conducted at the Sakarya Educational and Research Hospital. Prior approval from the Institutional Review Board was taken and written informed consent was obtained from the parents of each subject (IRB:71522473/050.01.04/68). The study was performed in adherence to the Declaration of Helsinki.

Patients diagnosed as RA, SLE, Sjogren syndrome, and other connective tissue diseases who applied to our clinic were recruited in this study. Exclusion criteria were any retinal disease, uveitis, 21mmHg and higher intraocular pressure (IOP), presence of glaucoma, spherical refractive disorders exceeding 6 diopters, cylindrical refraction above 3 diopters, any lens opacities, and previous intraocular or refractive surgery history.

The study group consisted of patients which have already used HCQ and have no additional disease and the control group consisted of patients who have not received HCQ treatment. The study group was subdivided into two groups according to HCQ usage time. The group 1 was composed of patients who have used this medicine at least 5 years and group 2 was composed of patients who have received this treatment for 1 to 5 years.

Full ophthalmic examination including best corrected visual acuity (BCVA) by Snellen chart, IOP measured with Goldmann Applanation Tonometer, and slit lamp evaluation were performed to all patients. Fundus evaluation was performed by using slit lamp biomicroscopy and + 90 diopter non-contact lens after pupil dilation. The RNFL thickness, CMT, and ganglion cell-inner plexiform layer (GC-IPL) thickness measurements of all patients were performed by using Cirrus EDI-OCT (Carl Zeiss Meditec, Dublin, CA, USA). 10 – 2 visual field test was performed with Humphrey field analyzer Standard Automated Perimetry, the 10–2 SITA FAST program (Humphrey Field analyzer, Carl Zeiss Meditec, Dublin, CA, USA) and FAF imaging by using Canon CX-1 Retinal Camera was done. Contrast sensitivity test was performed by using Tomey Chart Panel TCP-3000P (Tomey, Nurnberg, Germany). All these tests were performed by the same ophthalmologist (V.S.).

Cirrus EDI-OCT (Carl Zeiss Meditec, Dublin, CA, USA) has been used for peripapillary RNFL and GC-IPL thickness measurements. Mean RNFL thickness has been measured according to “Optic Disc Cube 200*200” method. In addition to that, ganglion cell analysis has been conducted in accordance with “Macular Cube 512*128” program. Mean and fragmented RNFL thickness, mean and six fragmented GC-IPL thicknesses have been evaluated. Central macular thickness was measured by using enhanced depth macular OCT (Macular Cube 512*128 scan protocol). The images with signal quality which were worse than 8/10 have been excluded. Scans with misalignment, segmentation failure, decentration of the measurement circle, poor illumination and the ones which were out of focus have also been excluded.

Standard Automated Perimetry, the 10–2 SITA FAST program (Humphrey Field analyzer, Carl Zeiss Meditec, Dublin, CA, USA) was used for visual field (VF) testing. Fixation losses more than 20%, false-positive and false-negative errors more than 33% were not accepted. The perimeter software was used to calculate mean deviation (MD) and pattern standard deviation (PSD). According to the scotoma assessment, VF tests were divided into 4 groups; 0: normal, 1: mild low sensitivity in any central visual field region, 2: paracentral scotoma with moderate low sensitivity, 3: paracentral scotoma with complete loss of sensitivity (11).

Fundus autofluorescence images were recorded at 530–580 nm wavelength and through a 640 nm barrier filter using the Canon CX-1 Digital Mydriatic Retinal Camera (Canon Inc.Tokyo). Those with low image quality were not included in the study. 5.5 mm between the upper and lower temporal arcade of macula in each image; the fovea was marked manually by the same ophthalmologist with an area of 1.5 mm, and each image was saved as a TIFF file with a 512x512 pixel 16-bit gray (Fig. 1). Autofluorescence images were recorded for each patient using the MATLAB 2013a software program (Maths Works Inc., Natick, MA) for mean pixel density and average curve amplitude.

Tomey chart panel TCP-300P was used for contrast sensitivity measurement. Contrast sensitivity test includes sine wave gratings at 5 spatial frequencies, each with 8 sensitivity levels. Contrast sensitivity tested for spatial frequencies of 1.5, 3, 6, 12, 18 cycles/ degree (cpd) at a distance of two meters and 50 centimeters. Contrast sensitivity test was applied to all patients after complete correction with glasses as it was affected by refraction. All tests were evaluated by the same observer in the same room (61 lux).

SPSS 23.0 package was used for statistical analysis of data. Categorical measurements were summarized as numbers and percentages, and numerical measurements as mean and standard deviation (mean and minimum-maximum where necessary). The compliance of the data to normal distribution Kolmogrov Smirnov and Shapino Wilk tests are examined. The Kruskal Wallis test was used to compare categorical measurements between groups. Mann Whitney U test was used to compare numerical measurements between groups. The statistical significance level was taken as 0.05 in all tests.

Results

60 eyes of 31 patients who had been using HCQ for more than five years were formed group 1; 62 eyes of 32 patients using drugs for less than 5 years (at least 1 year) were formed group 2. Control group was composed of 56 eyes of 28 patients with the same diagnoses without using medication.

In the first group, 27 (%87,1) were women, 4 (%12,9) were men; in the second group, 31 (%96,8) were women, 1 (%3,1) were men, and in the control group 26 (%92,8) were women and 2 (%7,2) were men. The mean age of the first group was 49.67 ± 8.25, the mean age of the second group was 49.92 ± 8.22, the average age of the control group was 46.93 ± 6.17 years, and no statistically significant difference was found between the average ages of the three groups. (p:0.066)

The diagnoses of the patients included in the study were SLE (%60,7), RA (%22,5), Sjogren (%12,4), Ankylosing Spondylitis (%1,1), Discoid Lupus (%1,1), Mixed Connective Tissue Disease (%1,1) and Antiphospholipid Syndrome (%1,1).

The HCQ usage period of the patients in group 1 was 8.77 ± 3.01 years; group 2 was 2.67 ± 1.09 years. The cumulative dose amounts they received were calculated as 639.97 ± 217.52 gr and 194.98 ± 79.57 gr. All patients have been taking 200 mg of HCQ daily in our study.

When the thickness analyzes of the patient and control groups were examined, it was found that the sectoral and mean GC-IPL thicknesses were statistically significant in the patient groups compared to the control group ($p < 0.05$**).** The ganglion layer thickness was thinner in all quadrants in patient groups (Table 1). When the groups were compared in pairs, a significant difference was found between group 2 and the control group in terms of superior and superior nasal quadrants of the GC-IPL ($p < 0.05$).

Table 1
GC-IPL thickness measurements of patient and control groups

GC-IPL thickness (μ)	Group 1	Group 2	Control	p value
Superior	84.03 ± 6.61	81.42 ± 9.84	85.79 ± 6.46	**0.034***
Superior nasal	83.35 ± 7.20	80.89 ± 11.17	86.09 ± 7.06	**0.011***
Superior temporal	79.72 ± 6.54	77.60 ± 10.78	82.82 ± 5.76	**0.004***
Inferior	80.40 ± 6.63	80.65 ± 10.05	84.84 ± 5.60	**0.003***
Inferior nazal	81.28 ± 7.70	80.98 ± 10.00	85.11 ± 7.25	**0.010***
Inferior temporal	80.55 ± 7.01	80.50 ± 8.99	82.68 ± 12.20	**0.038***
Mean	81.63 ± 5.41	80.35 ± 9.32	84.86 ± 5.64	**0.006***
p*<0.05, Kruskal Wallis test				

When the central macular thickness measurements of the patient and control groups were examined, it was observed that there was no statistically significant difference ($p > 0.673$). When the groups were compared in pairs, no significant difference was found ($p > 0.05$).

When the RNFL measurements of the groups were examined, temporal quadrant and mean RNFL thicknesses were statistically thinner in the patient groups than in the control group ($p < 0.05$).

When the RNFL measurements of the groups were examined, temporal quadrant and mean RNFL thicknesses were statistically thinner in the patient groups than in the control groups ($p < 0.05$, Table 2).

Table 2
RNFL measurements of patient and control groups

RNFL thickness (μ)	Group 1	Group 2	Control	p value
Superior	114.23 ± 14.95	113.52 ± 16.42	118.89 ± 15.45	0.163
Inferior	119.38 ± 14.94	118.48 ± 17.05	123.02 ± 14.78	0.229
Nasal	68.73 ± 9.45	69.16 ± 10.56	73.00 ± 3.43	0.241
Temporal	62.37 ± 9.62	60.76 ± 9.15	64.70 ± 7.25	0.031
Mean	91.07 ± 8.34	90.50 ± 10.65	94.98 ± 8.44	**0.026***
*p < 0.05, Kruskal Wallis test				

When the groups were compared in pairs, temporal and mean RNFL thicknesses were significantly thinner in Group 2 than in the control group ($p < 0.05$).

There was no statistically significant difference in MD and PSD between the three groups (p = 0.150, p = 0.105, Table 3). When MD and PSD measurements were compared between the groups in pairs, no significant difference was found (p > 0.05). When the visual field sensitivity was examined, a significant difference was found between the groups (p:0.028, Table 3).

Table 3
Visual field measurements of patient and control groups

Visual field measurements	MD	PSD	Normal	Mild low sensitivity	Paracentral scotoma with moderate low sensitivity	Paracentral scotoma with complete loss of sensitivity
Group 1	-3.78 ± 2.13	1.50 ± 0.66	23 (%38)	19 (%31)	10 (%16)	8 (%13)
Group 2	-3.07 ± 1.80	1.27 ± 0.36	36 (%58)	18 (%29)	8 (%12)	0 (%0)
Control	-3.02 ± 1.4	1.37 ± 0.50	37(%65c)	12 (%21)	7 (%12)	0 (%0)
p value	0.150	0.105	**0.028***			
*p < 0.05, Kruskal Wallis test, Chi-square test (Moderate low sensitivity and complete loss of sensitivity were combined)						

There was a statistically significant difference between groups in terms of the mean macular pixel density (p = 0.013, Table 4). When the groups were compared in pairs, a significant difference was found between Group 1 and the control group (p < 0.05). When the mean fovea pixel densities were evaluated, no significant difference was found between the three groups (p = 0.069, Table 4). When we compared the groups in pairs, no significant difference was seen (p > 0.05).

Table 4
Mean macular and fovea pixel density of patient and control groups

Pixel density	Group 1	Group 2	Control	p value
Mean macular	160.18 ± 26.81	156.80 ± 24.99	145.67 ± 27.50	**0.013***
Mean fovea	155.99 ± 27.77	152.96 ± 25.00	145.83 ± 25.17	0.069
*p < 0.05, Kruskal Wallis test				

When the contrast sensitivity measurements were compared, a statistically significant difference was found in all spatial frequencies except 6 and 18 cycles/degree (cpd) (p < 0.05, Table 5). When the groups

were compared in pairs, there was a significant difference between Group 1 and the control group at 3 and 12 cpd ($p < 0.05$). There was a significant difference between Group 2 and the control group at 1, 5 and 6 cpd ($p < 0.05$).

Table 5
Contrast sensitivity measurements of patient and control groups

Contrast sensitivity measurements (cpd)	Group 1	Group 2	Control	p value
1.5 cpd	39.78 ± 17.95	39.29 ± 13.94	54.77 ± 37.16	**0.003***
3 cpd	75.53 ± 41.95	76.79 ± 31.77	98.70 ± 49.19	**0.015***
6 cpd	81.53 ± 51.91	78.84 ± 43.79	94.38 ± 45.30	0.118
12 cpd	27.98 ± 24.22	29.74 ± 23.47	44.05 ± 38.87	**0.016***
18 cpd	10.85 ± 10.94	11.03 ± 6.96	12.54 ± 8.25	0.146
***p < 0.05, Kruskal Wallis test				

Discussion

In this study, patients who used HCQ for at least one year were divided into two groups according to the duration of drug use (Group 1 used more than five years, Group 2 used less than five years and compared with the control group patients who did not use drugs). RNFL, CMT, GCC thickness, FAF imaging, VF and contrast sensitivity measurements were compared statistically. The aim was to evaluate structural and functional measurement methods in detecting early retinal damage due to HCQ.

Bonanomi et al. study compared 34 patients who used antimalarial drugs and 34 healthy individuals who did not use drugs. RNFL thicknesses in all regions were found to be significantly lower in the patient group. Moreover, the effect of the cumulative dose of antimalarial drugs on RNFL was evaluated and no relationship was found (12). Pasahhika et al. found that RNFL thicknesses were thinner in patients using long-term antimalarial drugs (13). Antunes et al. conducted a study with 22 patients using antimalarial drugs at least one year for treatment of RA, and found a statistically significant correlation between the duration of drug use and thinning of RNFL thicknesses (14). In our study, the temporal quadrant and mean RNFL thicknesses were statistically lower in the groups using HCQ.

In the study conducted by Pasadhika et al., patients using chronic antimalarial drugs without clinical signs of toxicity compared with healthy individuals, and GCC thickness was found to be significantly thinner in the drug-using group (15). Kan et al. compared the control group with patients using the drugs for more than 5 years, whose visual acuity, fundus examination, visual field test were normal. As a result, mean, minimum, and sectoral GCC thicknesses were significantly lower in the patient group (16). Lee et al. found GCC thickness remarkably thin, in patients with HCQ retinopathy who had been exposed to a high cumulative dose. However, no significant correlation was observed between GCC thickness and the

cumulative dose of HCQ (17). In our study, the sectoral and mean GC-IPL thicknesses were significantly lower in the patients compared to the control group.

Pasadhika et al. compared the healthy group with patients using antimalarial drugs whose no evidence of retinal toxicity with a healthy group. No significant difference was found between the two groups in the thickness measurements of central macula and other layers of the macula (13). Marmor et al. conducted a study with 10 patients using the drugs for more than 6 years, who had suspicious defects in the visual field tests; found that macular thicknesses decreased in all quadrants and in total in all patients (18). In our study, there was no significant difference between the three groups. Difference in sample sizes might have affected the alterations.

Xiaoyun et al. found no significant difference in MD and PSD values between RA patients receiving antimalarial drugs and healthy groups (19). Lai et al. showed that no significant correlation between MD, PSD values and cumulative dose (20). On the other hand, Tanga et al. found that MD and PSD values were significantly lower in patients who used HCQ. These parameters were found to be significantly different in patients who received treatment for a longer period (21). In our study, there was no statistically significant difference in MD and PSD between the three groups (p:0.150). In addition, when MD and PSD measurements were compared in pairs, no significant difference was found (p > 0,05). However, a significant decrease in visual field sensitivity was found in the patient groups. We think that visual field sensitivity values may be a prognostic factor in detecting early retinal damage. For this reason, we should examine not only MD and PSD values but also VF sensitivity values.

Kellner S. et al. examined mfERG, FAF, SD-OCT imaging methods in 8 patients using antimalarial drugs and found changes in 5 of the patients. Pericentral hyper autofluorescence areas were recorded on FAF imaging in these patients (22). FAF imaging was evaluated in 25 patients using antimalarial drugs for a long time by Kellner ve Renner. In this study; FAF imaging indicated that there is a hyper autofluorescence appearance in the parafoveal area in the early retinopathy and a complete loss of autofluorescence in advanced retinopathy (23). In our study, when macula FAF images were compared, a statistically different was found between the three groups (p:0.013). The mean macula pixel density in the patient groups were found to be significantly higher than the control group. When the fovea mean pixel densities were examined, no significant difference was found between the three groups (p > 0.05). Our results were found to be compatible with literature and in our opinion, FAF imaging may be useful in detecting early retinal changes.

Salu et al. evaluated contrast sensitivity in 5 different spatial frequencies (1.5, 3, 6, 12, 18 c/d) under photopic and mesopic conditions in a patient with SLE with HCQ retinopathy. The results of the patient were compared with 10 healthy people in the same age group and were found to be significantly lower than the healthy group at all spatial frequencies (24). Bishara et al reported high frequency of pathological and suspicious contrast sensitivity tests in the medication group (25). The patients who used HCQ for an average 3 years and had normal fundus examination were compared with the healthy group by Tanga et al. In this study, contrast sensitivity was significantly lower in the group using HCQ

(21). Tığ et al. also stated that although visual acuity was normal in patients using HCQ, there might be a decrease in contrast sensitivity values (26). In our study, in all spatial frequencies except 6 and 8 cpd, statistically significant lower values were found in the patient groups compared to the control group ($p < 0,05$). The early effect of contrast sensitivity may be associated with ganglion and bipolar cell damage due to antimalarial drug use (27).

The relatively small sample size may be evaluated as the limitation of the current study. On the other hand, Matlab program was used for more reliable results in FAF evaluation. The control group of this current study was composed of patients with rheumatologic diseases. This eliminated the effect of these diseases on parameters.

In conclusion, mean and temporal quadrant RNFL thicknesses were statistically lower in the groups using HCQ. CMT values were not different between the patient and control groups. The sectoral and mean GC-IPL thicknesses were significantly lower in the patients compared to the control group. Although there was no significant difference in MD and PSD values in the visual field test, there was a decrease in VF sensitivity. Contrast sensitivity was lower in the patient groups. In the FAF imaging, mean macula pixel densities were higher in the patient groups than the control group, but mean fovea pixel densities were not different between the two groups. Functional tests and structural tests should be used together for the early detection of retinal damage due to using HCQ.

Declarations

Compliance with Ethical Standarts

Disclosure of potential conflict of interest: All authors declare that they have no conflict of interest.

Research involving Human Participants: Prior ethical approval from the Sakarya University Institutional Review Board (IRB: 71522473/050.01.04/68) was taken. The study was performed in adherence to the 1964 Declaration of Helsinki.

Informed Consent: Written informed consent was obtained from each subject, in the study.

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Consent to participate: Written informed consent was obtained from each subject in the study.

Consent for publication: Patients signed informed consent regarding publishing their data

Availability of data and material: not applicable

Code availability: not applicable

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Figures

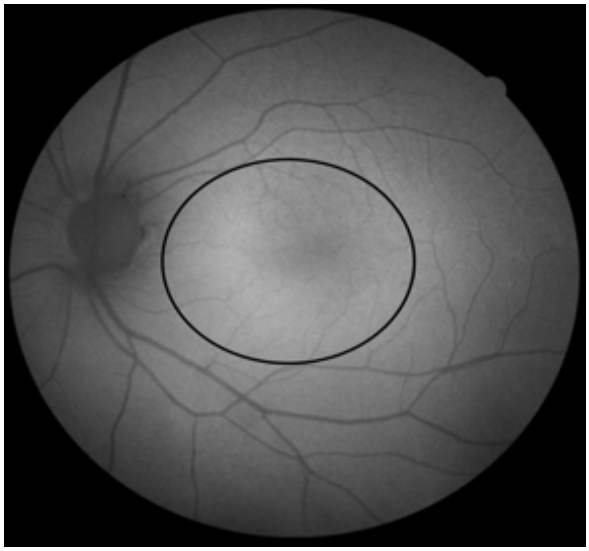

Figure 1

Marking of the macula on the Fundus Autofluorescence image